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Maternal and fetal plasma levels of free corticosteroids in pathological deliveries

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The corticosteroid level in umbilical blood shows large variations. Several factors affect this level: gestational age [13, 18, 19], type of delivery [5, 10, 19, 20] and the stress of delivery [3, 8, 13]. It is not certain; how far data obtained in animal experiments [2, 4, 9] can be applied to man. We do not know whether human delivery is also preceded by a rise in the fetal corticosteroid level as suggested by some [13, 14] or whether this rise is only a response of the fetal adrenal to intrauterine stress [16].

The concentration of free corticosteroids and the pH were determined during pathological deliveries to asses the effect of the fetal adrenal gland. Normal deliveries were used to obtain control values.

1 Material and method

We examined 41 mothers and their infants. A pathological delivery was diagnosed from the following criteria:

1. acidosis as determined from the pH
2. and/or an obstetric disease of mother or child.

Fetal blood was collected from the hyperemic fetal head skin according to SALING during delivery, and from the umbilical artery and vein between two ligatures, after birth. Maternal blood was taken from the cubital vein. In all 41 cases blood could be collected during delivery. In vaginal deliveries some could also be collected during the dilation and expulsion periods. Delivery was divided into the following stages:

EP 1 = early dilation period (cervix dilated 1—5 cm)
EP 2 = late dilation period (cervix dilated 6 to 10 cm)
AP = expulsion period (cervix fully dilated, head entering pelvis)
NA/NV = point of time of delivery: values of umbilical artery and vein.

The pH and free corticosteroids were determined in the blood; the latter according to MURPHY [12] using the competitive protein binding assay. The reliability of this method is $\pm 8.6\,\mu g$/100 ml with a probability error of less than 5% [17]. We examined 24 non-induced spontaneous vaginal deliveries, 8 forceps and 9 caesarean sections. Seven of the vaginal deliveries were premature, the gestational age of the infants being 31 to 37 weeks, 35 weeks on the average.

2 Results

Since the 41 cases had diverse pathologies and parameters were not equally distributed, there was no sense in obtaining mean values and standard deviations and to compare them with normal values. For the same reason the correlation coefficient between pH and corticosteroid levels was not calculated. Data are hence given graphically and individual values are shown in the tables as obtained at the moment of birth.

2.1 Vaginal spontaneous deliveries

Corticosteroids (CS) were determined at the time of birth in 24 pathological cases and in

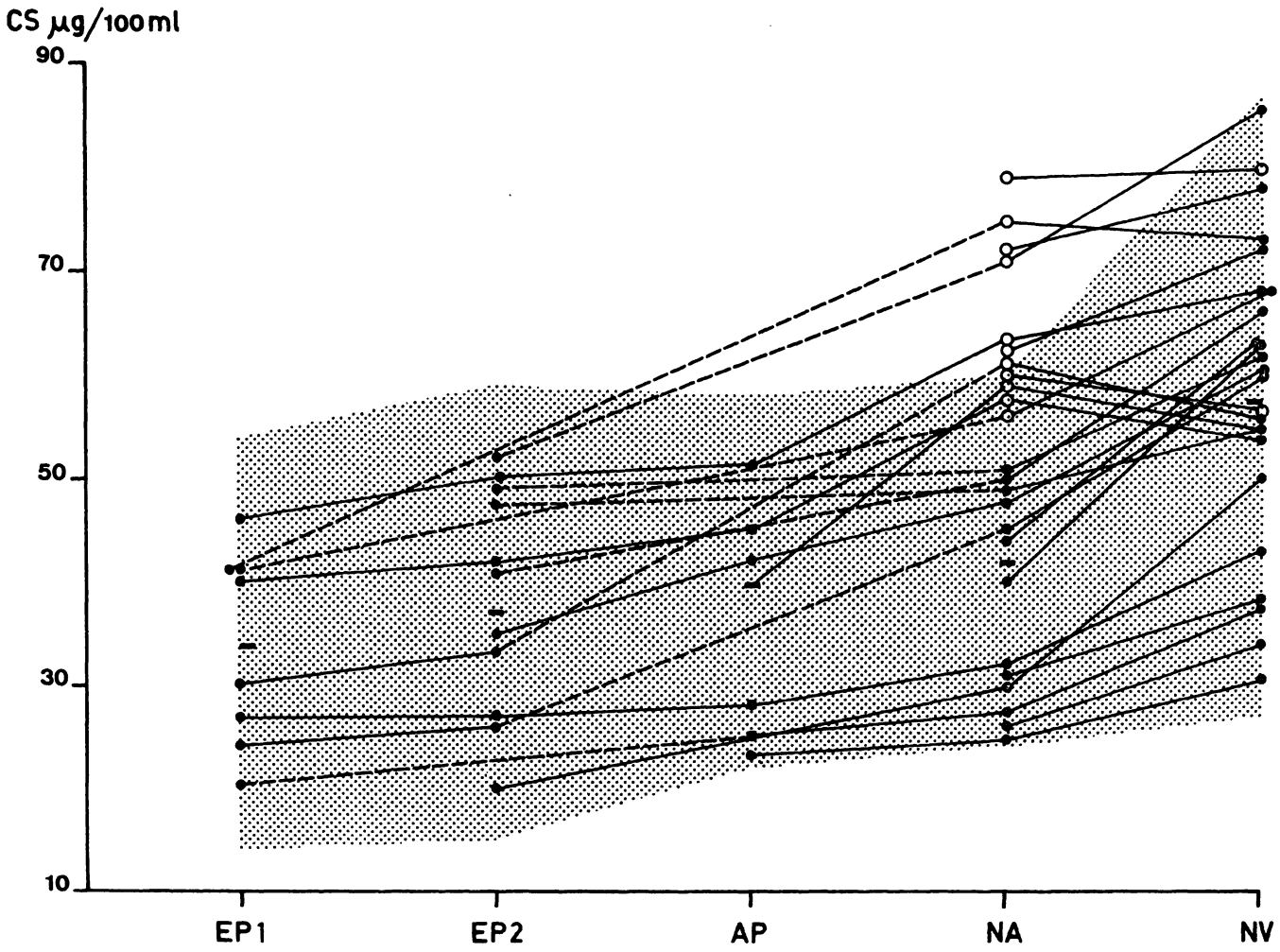

Fig. 1. Concentration of free corticosteroids (CS µg/100 ml) in fetal plasma in 24 vaginal deliveries.
Pointed areas = normal range with mean values (black line)
points = actual pH-values > 7.20 circle = actual pH-values < 7.20.

some also during delivery (Fig. 1). A continuous rise was found, as in normal deliveries and levels were the same as for normal births. If acidosis occurs the normal level is usually exceeded. Acidosis occurred during the last stage of labor. All deliveries were routinely controlled by microblood analyses during the last stages of labor.

Table I gives individual values at the time of delivery of pH and CS concentrations in maternal and umbilical plasma and also the arterio-venous difference in corticosteroid concentration. In the first eleven cases with a pH value below 7.2, the CS level was outside the normal range in 7 cases and within it in four. Values in the umbilical vein, however, are all normal. Only one mother had 97 µg/100 ml, which is just above the maternal norm.

In cases 12 to 18 with a pH above 7.2 in the umbilical artery, both fetal and maternal values were normal.

In premature deliveries, cases 19 to 24; with normal pH, the CS levels were lower than in term babies. This, however, is not statistically significant. Case 9 shows that the CS level can also rise in acidosis in the premature. The a—v difference of CS is usually decreased in acidosis; sometimes even to a negative value. The normal difference is 15 ± 5 µg/100 ml.

2.2 Delivery by forceps

Forceps were used under general anesthesia with nitrous oxide and Fluothane. In 4 cases such delivery was indicated by fetal acidosis, in two by preacidosis and in 2 because of severe late deceleration with normal pH. In 5 of the 8 cases

Tab. I. Values of pH and free corticosteroids (CS μg/100 ml) in the umbilical artery (UA), vein (UV) and maternal vein and the a—v difference. 24 spontaneous deliveries; EPH = EPH gestosis; visible constriction with cord = VC; meconium = Mec; T + = postmature; PM = premature.

case	diagnosis	UA		UV		mother		⊿CS
		pH_{act}	CS	pH_{act}	CS	pH_{act}	CS	UA—UV
1	EPH	7.081	60	7.156	57	7.421	70	—3
2	EPH	7.090	79	7.188	80	7.345	86	1
3	Mec	7.128	61	7.274	56	7.363	78	—5
4	VC	7.131	75	7.268	73	7.389	92	—2
5	EPH	7.159	58	7.314	54	7.424	68	—4
6	VC	7.161	56	7.398	68	7.471	83	12
7	EPH	7.170	72	7.288	78	7.385	97	6
8	Mec	7.180	62	7.307	72	7.389	85	10
9	PM/VC	7.181	59	7.232	55	7.455	75	—4
10	Mec	7.184	72	7.246	86	7.356	91	14
11	Mec	7.198	63	7.307	68	7.395	84	5
12	VC	7.215	51	7.279	62	7.387	78	11
13	T +	7.256	49	7.290	55	7.308	66	6
14	T +	7.258	32	7.280	43	7.496	52	11
15	VC/Mec	7.259	45	7.341	60	7.431	70	15
16	T +	7.280	28	7.294	38	7.396	48	10
17	T +	7.294	40	7.347	63	7.398	77	23
18	T +	7.371	50	7.398	66	7.450	86	16
19	PM/EPH	7.278	44	7.314	63	7.376	66	19
20	PM/EPH	7.301	48	7.352	60	7.362	70	12
21	PM/Mec	7.320	31	7.335	36	7.412	50	5
22	PM/EPH	7.328	30	7.375	50	7.441	54	20
23	PM/EPH	7.332	26	7.394	34	7.436	50	8
24	PM/VC	7.345	25	7.442	31	7.592	45	6
1—11 NA-pH $<$ 7.20	mean		65		68		82	2.7
12—18 NA-pH $>$ 7.20	mean		42		55		67	13
19—24 PM	mean		34		48		56	11.7

Tab. II. 8 deliveries by forceps (see legend in Tab. I).

case	UA		UV		mother		⊿CS
	pH_{act}	CS	pH_{act}	CS	pH_{act}	CS	UA—UV
1	7.053	75	7.169	83	7.394	84	8
2	7.087	62	7.160	73	7.409	83	11
3	7.088	64	7.179	58	7.406	76	—6
4	7.090	79	7.190	80	7.378	88	1
5	7.104	63	7.191	65	7.395	76	2
6	7.157	62	7.207	69	7.387	80	7
7	7.160	50	7.178	53	7.254	75	3
8	7.235	46	7.287	54	7.296	64	8
1—8 mean		63		67		78	4.2

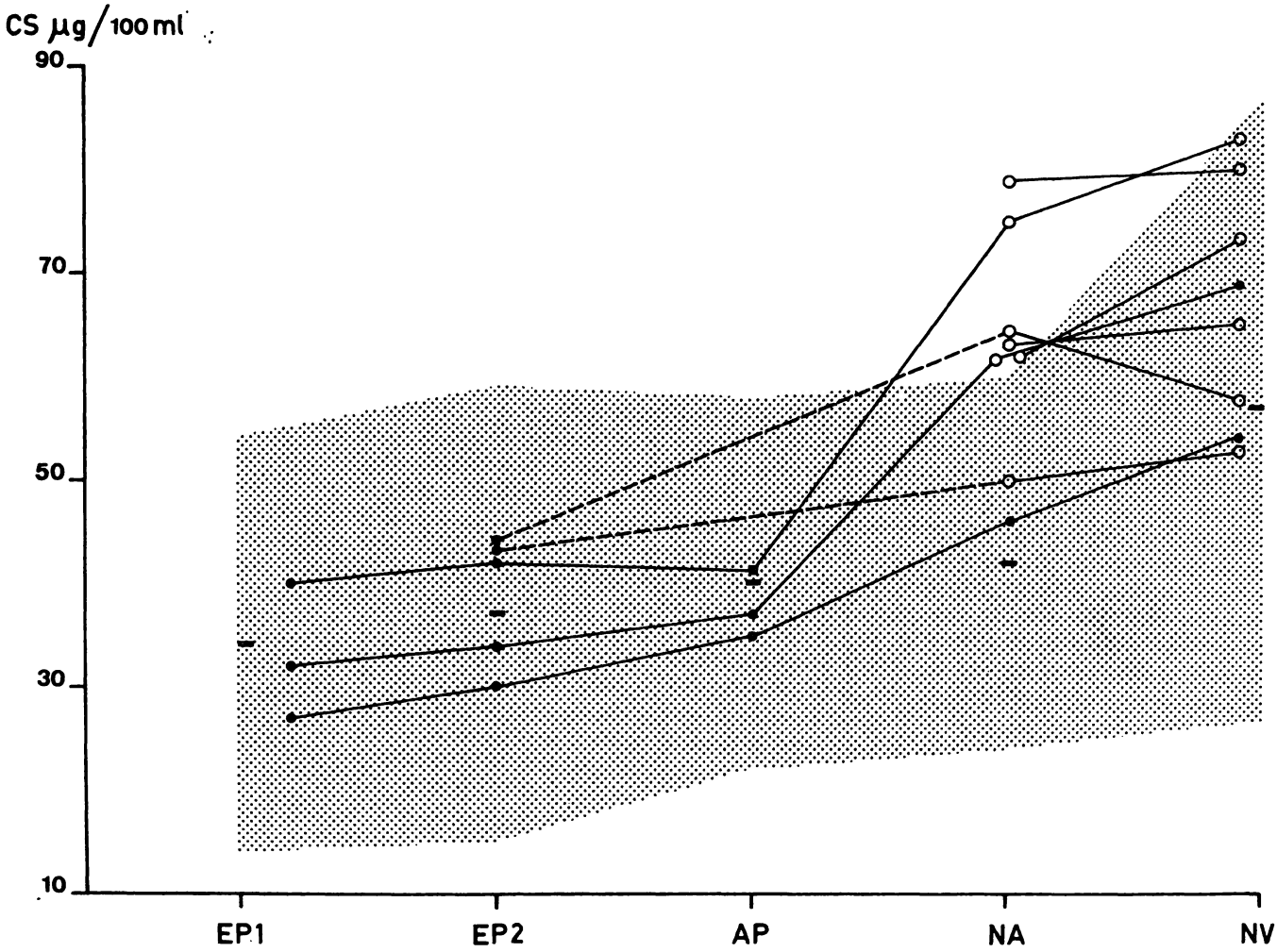

Fig. 2. Concentration of free corticosteroids (CS µg/100 ml) in fetal plasma in 8 deliveries by forceps (see legend of Fig. 1).

Tab. III: 9 cases of caesarean section (see legends in Tab. I).

Case	diagnosis	Caesarian section	UA		UV		mother		Δ CS
			pH_{act}	CS	pH_{act}	CS	pH_{act}	CS	UA—UV
1	Acidosis	secundary	7.054	63	7.138	65	7.354	80	2
2	Acidosis	secundary	7.100	63	7.180	63	7.370	72	0
3	T +/Mec	primary	7.213	47	7.247	52	7.374	60	5
4	induction of labor	secundary	7.222	45	7.297	63	7.341	80	18
5	EPH/Pre-acidosis	secundary	7.223	59	7.281	68	7.470	83	9
6	Pre-acidosis	secundary	7.245	36	7.309	42	7.384	47	6
7	small-for-date	primary	7.250	61	7.293	88	7.395	97	27
8	Breech pres. EPH	primary	7.297	53	7.288	72	7.365	83	19
9	Mec/late decelerations	secundary	7.317	40	7.369	53	7.392	67	13
1 + 2	mean			63		64		76	1
3 — 9	mean			48		62		74	14

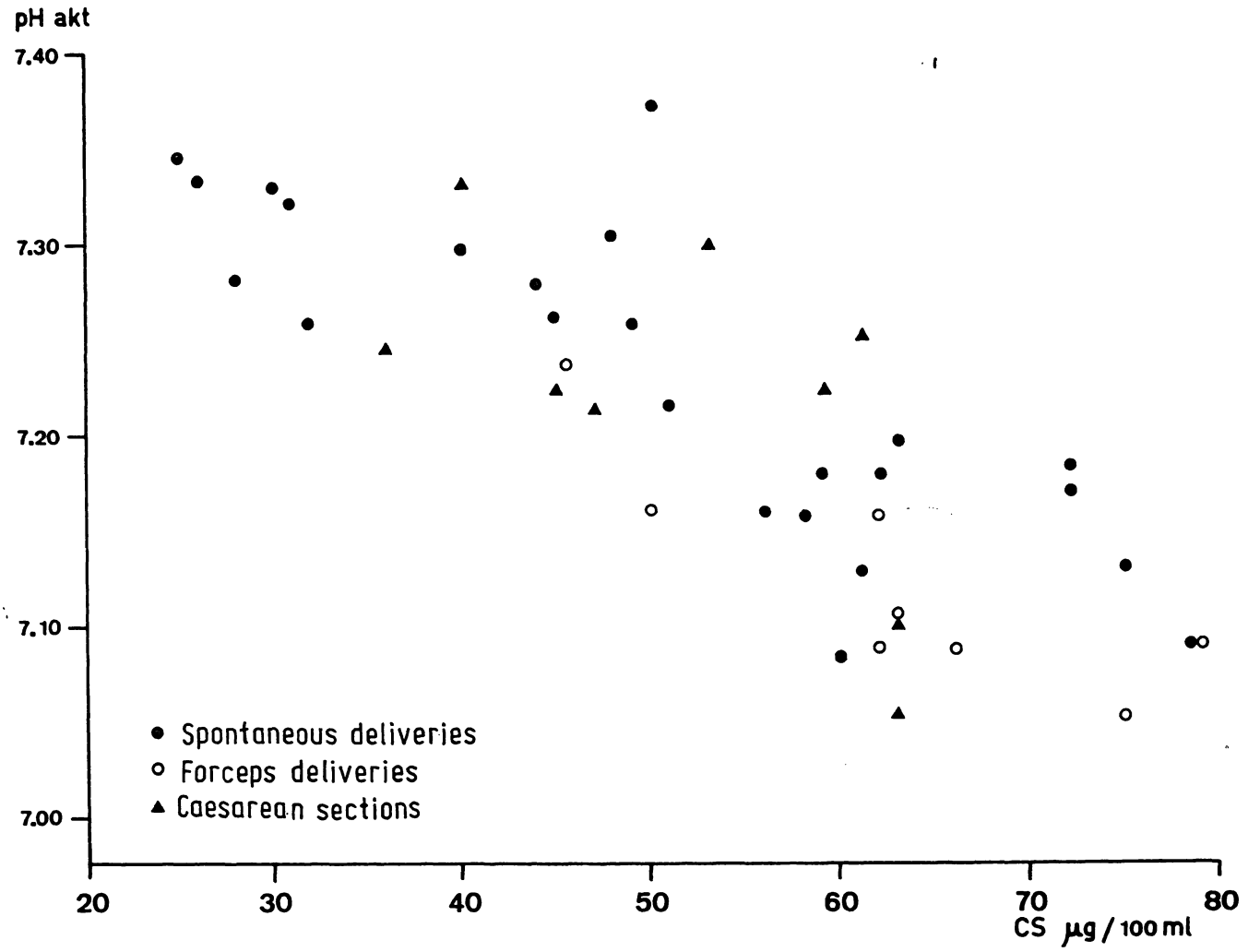

Fig. 3. Concentration of free corticosteroids in the plasma of umbilical artery in relation to the actual pH-value.

CS levels were also determined during labor (Fig. 2). Except for one case; CS values were outside the normal range in acidosis.

Values in the umbilical vein were in the upper normal range and they were normal in the maternal artery (Tab. II). The mean a—v CS difference is lower than normal.

2.3 Caesarean section

In 9 cases only blood collected at delivery could be analyzed (Tab. III). In 3 cases section was commenced before the initiation of labor. Data from cases 3 and 8 do not differ from those obtained in spontaneous deliveries. In case 7 the CS concentration in both mother and fetus are outside the normal values; even though there is no acidosis present. In 6 patients sections were performed in the last stage of labor. In two cases in whom acidosis in the umbilical artery could be found, the CS concentration was outside the normal range. The a—v difference was 0 µg/100 ml in one and 2 µg/100 ml in the other case. If the pH is above 7.2 CS levels are the same as in normal deliveries.

Fig. 3 shows the relationship between the pH and the CS blood level in the umbilical artery for all 41 cases. There is an inverse relation. This trend is independent of the type of delivery.

3 Discussion

The level of free CS rises in maternal and umbilical plasma with increasing gestational age [11, 13, 18]. A further rise is seen during labor and delivery [15]. We showed that this rise also occurs in fetal blood from the head [17]. At the end of delivery we found a mean of 42 µg/

100 ml steroids with transcortin affinity in the umbilical artery. This is much lower than reported by KRAUER [8]. Since progesterone is also determined by our technique; we have higher values than SMITH and SHEARMAN [18]. The progesterone level remains unchanged during labor [7, 15] and hence we conclude that the rise is due to CS. The CS concentration in maternal and fetal blood also depends on the type of delivery. Values are higher after vaginal delivery than after cesarean sections commenced before the intiation of labor [8, 13, 16, 19]. However, if sections were started after labor had commenced, differences were minimal [19]. The highest values were found after the use of forceps [8]. These differences were found for both total steroids [8, 19] and individual adrenal corticosteroids [3, 5, 10, 13, 20]. These data were thought to indicate an active role of the fetal adrenal cortex in the initiation of labor [13, 14, 18]. The rise in fetal CS shown in animals has not been demonstrated in man. **Perhaps it represents, depending on the type of delivery, a fetal response to the stress of delivery** [16, 20].

Adrenocorticosteroids are differently distributed in fetal and maternal blood. In adults cortisol is quantitatively the most important. In fetal blood there is an equal amount or more cortisone [3, 13, 20] and also more corticosterone [6]. MURPHY et al. [13] found 3 times as much cortisol in the umbilical artery as in the umbilical vein; while no difference was found by others [3]. Steroid metabolism in the fetus differs from that of the adult mainly because of increased or decreased enzyme activities [21].

These feto-maternal differences and the difficulty in determining the origin of fetal corticosteroids (maternal, placental, fetal) made it appear reasonable to determine total corticosteroid concentrations; e. g. during fetal hypoxia. A rise in the ACTH and a smaller one in the CS concentration in fetal sheep blood could be demonstrated during hypoxia [1].

We found a mean concentration of CS above the normal range in the umbilical artery in the presence of fetal acidosis. A fall in the a—v difference was noted at the same time. These changes depend on the fetal pH and not on the mode of delivery. In cases of fetal acidosis after spontaneous deliveries a smaller rise in CS levels was found in the umbilical vein and maternal plasma. No differences were seen between caesarean and forceps deliveries. Thus we may conclude that the fetal adrenal gland secretes more corticosteroids if intrauterine acidosis occurs.

Our results confirm those of others [13, 16, 18] who report that **in premature deliveries the CS levels in maternal and umbilical blood are lower than at term.** Nevertheless it appears that also in these cases the fetal adrenal gland reacts to fetal acidosis by secreting more steroids.

Summary

Does intrauterine acidosis induce increased steroid secretion? The concentration of free steroids (CS) increases in both fetal and maternal plasma during labor and delivery. Fetal levels are higher after vaginal than after cesarean section. These differences may indicate an important role of the fetal adrenal gland in the induction of labor or they may reflext merely the fetal response to the stress of delivery. During incrased intrauterine stress steroid secretion is increased as shown here.

We examined 41 mothers and their infants during pathological labor. Pathology was assessed from fetal acidosis and/or a clinically obstetric disease of the mother or fetus. The 41 cases included 9 cesarean sections, 8 forceps deliveries; 24 spontaneous deliveries of which 7 were premature. At the time of delivery the pH and CS level were determined in maternal and umbilical vessels in all cases. During spontaneous labor blood samples were also taken during the different stages of labour.

A competetive protein binding assay with transcortin without fractionation of the steroids was used. Progesteron was determined by the same assay. The level of this hormone, however, remains unchanged and hence any changes reflect changes in CS. The levels of CS were correlated with the pH values and compared to previously obtained normal values.

During pathological deliveries CS levels in both mother and fetus are normal as long as there is no acidosis **(Fig. 1)**. If acidosis is present the CS level in the umbilical artery is usually higher than normal. In 13 out of 18 vaginal deliveries the CS level was above normal, in the other 5 at the upper limit of normal **(Fig. 1 and 2)**. At the same time the a—v difference becomes smaller and sometimes even

negative. No changes were noted in maternal and umbilical venous blood **(Tab. I and II).** Similar dependence on the pH was found for cesarean sections **(Tab. III).** In premature deliveries without acidosis in the umbilical artery the CS levels were lower in both mother and fetus **(Tab. I).**

These results indicate that the fetal adrenal gland reacts to acidosis, i. e., intrauterine stress, with increased corticosteroid secretion. This rise depends on the pH of fetal blood and not on the type of delivery (Fig. 3).

Keywords: Acidosis, cesarean section, fetal adrenal gland, forceps, free corticosteroids, vaginal spontaneous delivery.

Zusammenfassung

Die Konzentration freier Kortikosteroide im fetalen und mütterlichen Plasma bei pathologischen Geburten

Reagiert der Fet bei einer intrauterinen Azidose mit einer gesteigerten Steroidsekretion? Die Konzentration freier Kortikosteroide nimmt während des Geburtsvorganges im mütterlichen und fetalen Plasma zu. Die fetalen Steroidkonzentrationen sind nach vaginalen Entbindungen höher als nach primärer Sectio caesarea. Diese Unterschiede könnten einerseits darauf hinweisen, daß die humane fetale Nebenniere eine wichtige Rolle bei der Geburtsauslösung spielt. Sie könnten jedoch anderseits lediglich der Ausdruck einer fetalen Antwort auf den Geburtsstreß sein. Bei einer verstärkten intrauterinen Streßsituation, nachgeweisen durch eine Azidose, müßte dann die Steroidkonzentration stärker ansteigen. Die Arbeit versucht die letztere Alternative zu beantworten.

Untersucht wurden 41 Mütter und deren Kinder während pathologischer Geburten. Die Pathologie äußerte sich im Auftreten einer fetalen Azidose und/oder im Vorliegen einer klinisch-geburtshilflichen Erkrankung der Mutter oder des Feten. Die 41 Fälle unterteilen sich in 9 Sectio caesarea, 8 Forzepsentbindungen und 24 Spontangeburten, davon 7 Frühgeburten. Bei allen Fällen konnte zum Zeitpunkt der Geburt bei der Mutter und in den Nabelgefäßen der aktuelle pH-Wert und die Konzentration freier Kortikosteroide gemessen werden, bei den vaginalen Entbindungen teilweise auch während der Eröffnungs- und Austreibungsperiode.

Als Bestimmungsmethode diente eine Competitive protein binding assay mit Transkortin ohne Steroidfraktionierung. Dabei wurde Progesteron miterfaßt. Da dessen Konzentration unter der Geburt jedoch nicht zunimmt, bedeutet ein Anstieg der Meßwerte eine Zunahme der Kortikosteroide. Im mütterlichen und fetalen Plasma liegen gänzlich verschiedenen Konzentrationsverhältnisse der einzelnen Kortikosteroide vor. Da die Bestimmung einzelner Kortikosteroide die Beantwortung der Fragestellung erschweren würde, verzichteten wir auf eine Steroidfraktionierung. Die gemessenen Konzentrationen der transkortin-affinen Steroidhormone wurden in Beziehung gesetzt zum aktuellen pH-Wert und verglichen mit dem in einer früheren Arbeit mitgeteilten Normalbereich.

Die Veränderungen der Kortikosteroidkonzentration unterscheiden sich bei pathologischen Geburten weder bei der Mutter noch beim Feten von denen beim normalen Geburtsablauf, sofern eine fetale Azidose fehlte **(Abb. 1).** Bei Auftreten einer Azidose überschreitet jedoch die CS-Konzentration der Nabelarterie in der Regel den Normalbereich. Bei 18 vaginalen Entbindungen, einschließlich der Forzepsgeburten, bei denen in der Nabelarterie ein pH-Wert unter 7,20 festgestellt wurde, lag die Kortikosteroidkonzentration in 13 Fällen oberhalb der Norm, in den restlichen 5 Fällen im obersten Normalbereich **(Abb. 1 und 2).** Gleichzeitig verminderten sich die arteriovenösen Differenzen, die bei einigen Fällen sogar negativ wurden. Die Werte im Nabelvenen- und im mütterlichen Plasma waren gegenüber Normalfällen nur geringgradig erhöht, überstiegen jedoch den Normbereich nicht **(Tab. I und II).**

Die gleichen Veränderungen konnten bei den Sectio-caesarea-Fällen festgestellt werden, je nachdem ob eine Azidose in der Nabelarterie gemessen werden konnte oder nicht **(Tab. III).** Bei Frühgeburten, die vaginal entbunden wurden und bei denen keine fetale Azidose vorlag, finden sich durchschnittlich tiefere CS-Konzentrationen bei Mutter und Fetus **(Tab. I).**

Diese Ergebnisse erlauben die Feststellung, daß die fetale Nebenniere bei Auftreten einer Azidose — im Sinne einer intrauterinen Streßsituation — mit einer vermehrten Ausschüttung von Kortikosteroiden reagiert. Der Konzentrationsanstieg ist dabei abhängig vom fetalen pH-Wert, nicht jedoch von der Art der Geburtsbeendigung (Abb. 3).

Schlüsselwörter: Azidose, fetale Nebenniere, Forzeps, freie Kortikosteroide, Sectio caesarea, vaginale Spontangeburten.

Résumé

Concentration de corticosteroides libres dans le plasma foetal et maternel en cas d'accouchement pathologique

En cas d'acidose intra-utérine, le foetus réagit-il par un accroissement de la sécrétion de stéroides? La concentration de corticostéroides libres augmente dans le plasma foetal et maternel pendant l'accouchement. Les concentrations de stéroides foetales sont plus élevées après accouchement vaginal qu'à la suite d'une section césarienne primaire. Ces différences pourraient donner à supposer, d'une part, que la glande surrénale du foetus humain joue un rôle important dans le déclenchement de l'accouchement, mais il est possible, par ailleurs, qu'elles soient uniquement le résultat d'une réaction foetale au travail de l'accouchement. En cas donc d'un stress intra-utérin particulièrement fort, avec, pour conséquence, une acidose, on devrait pouvoir observer une hausse de la concentration de stéroides. C'est à cette dernière alternative que le présent article tente d'apporter une reponse.

L'examen a porté sur 41 mères et leurs enfants en cours d'accouchement pathologique. Le caractère pathologique de ces accouchements se manifesta par l'apparition d'une acidose foetale et/ou la présence d'une maladie clinico-gynécologique de la mère ou du foetus. Ces 41 cas se sont répartis en 9 sections césariennes, 8 accouchements avec forceps et 24 accouchements spontanés dont 7 prématurés. Dans tous les cas il a été possible de mesurer la valeur actuelle du pH et la concentration de corticostéroides libres chez la mère et dans les vaisseaux ombilicaux au moment de la naissance et même aussi partiellement, pour les accouchements vaginaux, durant la période d'ouverture et d'explusion.

La méthode d'estimation utilisée a été un competitive protein binding assay avec transcortine sans fractionnement de stéroides. La progestérone a été également enregistrée et sa concentration n'augmentant pas pendant l'accouchement, la hausse des valeurs de mesure témoigne donc d'un accroissement des corticostéroides. On observe dans le plasma maternel et le plasma foetal des rapports den concentration des divers corticostéroides entièrement différents. Et comme l'estimation des divers corticostéroides rendrait la solution du problème plus difficile, nous avons renoncé à fractionner les stéroides. Les concentrations mesurées des hormones stéroides ayant une affinité avec la transcortine ont été rapportées à la valeur actuelle du pH et comparées aux normes établies dans une étude antérieure.

Dans les accouchements pathologiques, les changements de concentration de corticostéroides ne se différencient ni chez la mère ni chez le foetus de celles des acouchements normaux à condition d'absence d'acidose foetale **(Fig. 1)**. En cas d'acidose par contre, la concentration des corticostéroides de l'artère ombilicale dépasse en général la norme. Dans 18 accouchements vaginaux, y compris ceux avec forceps, où on a enregistré dans l'artère mobilicale une valeur de pH inférieure à 7,20, la concentration de corticostéroides dépassa la norme dans 13 cas, et se situa, dans les 5 autres cas, au niveau supérieur de la norme **(Fig. 1 et 2)**. En même temps on releva une réduction des différences artério-veineuses qui ont même été négatives dans quelques cas. Les valeurs enregistrées dans le plasma maternel et dans la veine ombilicale dépassèrent de peu seulement celles des cas normaux sans déborder toutefois le niveau normal **(Tab. I et II)**.

Les mêmes changements ont pu être observés dans les cas de section césarienne que l'on ait ou non enregistré de l'acidose dans l'artère ombilicale **(Tab. III)**.

Dans les accouchements prématurés vaginaux et avec absence d'acidose foetale, on a relevé des concentrations de corticostéroides en moyenne plus basses chez la mère comme chez le foetus **(Tab. I)**.

Ces résultats permettent de conclure que la glande surrénale foetale réagit en cas d'acidose — dans le sens d'un stress intrautérin — par une augmentation de la sécrétion de corticostéroides —. La hausse de concentration dépend ici de la valeur de pH du foetus mais non du processus terminal de l'accouchement (Fig. 3).

Mots-clés: Accouchements spontanés vaginaux, acidose, corticostéroides libres, forceps, glande surrénale foetale, section césarienne.

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